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# Management of BK Virus Nephropathy with IVIG in a Kidney Transplant Recipient Unresponsive to Immunosuppression Reduction

# BK Virüs Nefropatisinin İmmünsüpresyon Azaltımına Yanıtsız Bir Böbrek Nakli Alıcısında IVIG ile Tedavisi

# Eren et al. BK Virus Nephropathy Treatment with IVIG

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## Abstract
BK virus (BKV)-associated nephropathy (BKVN) is a complication that can lead to graft loss after kidney transplantation. The primary approach to this disease is reduction of immunosuppressive therapy; however, some cases are non-responsive to this strategy. This case report presents a patient with BKVN that was non-responsive to immunosuppressive reduction and was treated with intravenous immunoglobulin (IVIG). A 62-year-old male patient with a history of kidney transplantation from a living donor 2 years earlier presented with deterioration of renal function. High BKV loads were detected, and the diagnosis of BKVN was confirmed by renal biopsy. Despite discontinuation of mycophenolate mofetil, the viral load continued to increase, and graft function continued to deteriorate. Subsequently, the patient was treated with IVIG. BKV levels in plasma and urine decreased, but renal function showed only minimal improvement. This case highlights the effectiveness of IVIG in resistant BKVN and underscores the role of proactive screening methods in preventing graft rejection.
**Keywords:** Nephropathy, renal transplantation, BK virus, IVIG

## ÖZET
BK virüsü ile ilişkili nefropati (BKVN), böbrek nakli sonrası greft kaybına yol açabilen bir komplikasyondur. Bu hastalığa yönelik önceki yaklaşım, immünosüpresif tedavinin azaltılmasıdır, ancak bazı vakalar bu yaklaşıma yanıt vermemektedir. Bu vaka sunumu, immünosüpresif tedavinin azaltılmasına yanıt vermeyen ve intravenöz immünoglobulin (IVIG) ile tedavi edilen BKVN'li bir hastayı sunmaktadır. İki yıl önce canlı donörden böbrek nakli öyküsü olan 62 yaşındaki erkek hasta, böbrek fonksiyonlarında bozulma ile başvurdu. Yüksek BK virüsü (BKV) yükü tespit edildi ve böbrek biyopsisi ile BKVN tanısı doğrulandı. Mikofenolat mofetil kesilmesine rağmen viral yük artmaya ve greft fonksiyonu bozulmaya devam etti. Bunun üzerine hasta IVIG ile tedavi edildi. Plazma ve idrardaki BKV düzeyleri azaldı, ancak böbrek fonksiyonlarında minimal bir iyileşme görüldü. Bu vaka, dirençli BKVN'de IVIG'nin etkinliğini ve greft reddini önlemede proaktif tarama yöntemlerinin rolünü göstermektedir.
**Anahtar Kelimeler:** Nefropati, böbrek nakli, BK virüsü, IVIG

## Introduction
Chronic kidney disease is a global health issue that causes significant morbidity and mortality worldwide[1]. Kidney transplantation is considered the most effective treatment method in terms of survival and quality of life for patients with end-stage renal disease[2]. Kidney transplant recipients must receive regular immunosuppressive therapy to prevent graft rejection. These treatment regimens typically include

a combination of calcineurin inhibitors, such as tacrolimus, antiproliferative agents such as mycophenolate mofetil (MMF), and steroids. However, this potent immunosuppression renders patients vulnerable to opportunistic infections, particularly viral infections[3].

BK virus (BKV) is a polyomavirus that is common in the human population and usually remains latent. Reactivation of BKV in immunosuppressed kidney transplant recipients can lead to viral replication in renal tubular epithelial cells and potentially result in BKV-associated nephropathy (BKVN). BKVN is a complication that can lead to progressive graft dysfunction, interstitial nephritis, and graft loss[4].

The primary approach to managing BKVN is the reduction of immunosuppressive therapy. The main goal of this strategy is to enable the immune system to control viral replication. However, this approach requires a balance between BKV clearance and the risk of graft rejection. Treatment options are limited in refractory cases because there is no specific antiviral agent with proven efficacy. In such cases, the role of intravenous immunoglobulin (IVIG) is being investigated. The immunomodulatory effects of IVIG and its potential to contain neutralizing antibodies against BKV make it a possible treatment option for refractory BKVN[5]. In this case, we aimed to discuss the efficacy and outcomes of IVIG treatment in a patient with BKVN who did not respond to standard immunosuppression reduction therapy.

## Case Report

A 62-year-old male patient was admitted to the nephrology clinic with a history of kidney transplantation from a living donor two years earlier. The patient had diabetes mellitus, hypertension, and gout. He had not attended routine follow-up appointments for approximately one year. Laboratory tests performed at presentation showed an increase in baseline creatinine from 1.0 to 1.95 mg/dL.

Because of this deterioration, the patient was evaluated for possible causes of kidney dysfunction. He did not report any recent oral intake problems or diarrhea. There was no history of contrast imaging within the previous month. No new medications or herbal products were reported. Blood glucose and blood pressure measurements were within normal limits before and during hospitalization. The results for other viral infectious agents that could cause kidney dysfunction were negative. The patient's tacrolimus level was low (3.42 µg/L), and the dose was adjusted accordingly. The patient was initially evaluated with a preliminary diagnosis of graft rejection. BKV polymerase chain reaction (PCR) positivity was detected at a level of 12,747,732,633 copies/mL in urine and 987,870 copies/mL in plasma. The pathological examination of the renal allograft biopsy performed to confirm the diagnosis was reported as consistent with BKVN. Figures 1 and 2 show the examination of slides stained with hematoxylin and eosin, whereas Figure 3 shows the examination performed using immunohistochemical markers.

The patient was receiving standard triple immunosuppressive therapy, including tacrolimus, MMF, and prednisolone, after kidney transplantation. Following the diagnosis of BKVN, MMF therapy was discontinued to reduce immunosuppression. After this intervention, a temporary decline in BKV levels was observed (urine: 4,666,376,864 copies/mL; plasma: 202,969 copies/mL). However, in subsequent follow-ups, the patient's BKV viral load increased again (urine: 6,656,038,735 copies/mL; plasma: 413,255 copies/mL), and renal function tests progressively deteriorated (creatinine: 3.15 mg/dL).

As this condition remained unresponsive to immunosuppression reduction, the patient was administered IVIG at a dose of 300 mg/kg for a total of four doses as adjuvant therapy. A decline in BKV levels was observed after IVIG treatment (urine: 973,615,474 copies/mL; plasma: 162,790 copies/mL), and partial improvement was achieved in renal function (creatinine: 2.8 mg/dL). The patient's laboratory results are presented in Table 1.

## Discussion

This case demonstrates the complexity and challenges involved in managing BKVN after kidney transplantation. In our patient, the failure to control BKV replication and the progressive deterioration of renal function despite discontinuation of MMF, one of the mainstays of immunosuppressive therapy, highlight how difficult the treatment of this disease can be. The most fundamental challenge in BKV treatment is the need to suppress viral replication by allowing an immune response while simultaneously avoiding allograft rejection[5].

Another important factor that negatively affected the course of this case was the patient's late presentation, after significant deterioration in renal function and lack of routine follow-up. Current clinical guidelines recommend regular screening of kidney transplant recipients, particularly within the first 1–2 years, to detect BKV reactivation at an early stage[4]. This screening is usually performed using plasma BKV PCR testing, with the aim of detecting viremia before graft dysfunction develops and initiating preemptive immunosuppression reduction. Early intervention significantly reduces progression to BKVN and the associated risk of irreversible fibrosis[6].

Reduction of immunosuppression, particularly discontinuation of antiproliferative agents, is considered the first-line treatment for BKVN. However, this approach places patients at risk of T-cell-mediated or antibody-mediated rejection. Studies have reported that acute rejection rates in patients whose immunosuppression was reduced after BKVN diagnosis range from 8% to 12%[7]. Therefore, viral load and graft function should be closely monitored.

In cases unresponsive to standard treatment, various adjuvant therapies, whose efficacy and safety have not been established in randomized controlled trials, have been explored. Although agents such as leflunomide, cidofovir, and fluoroquinolones have been used in different studies, their inconsistent success rates and potential side effects (e.g., nephrotoxicity associated with cidofovir) limit their use[4]. In this context, IVIG therapy emerges as a potential option, particularly in cases where immunosuppression cannot be further reduced or remains ineffective. Although the mechanism of action of IVIG is not fully understood, it is thought to exert a direct antiviral effect through neutralizing antibodies against BKV and to modulate T- and B-cell responses through its broad immunomodulatory properties[8]. In our case, a decrease in BKV loads in plasma and urine was observed after IVIG treatment. This virological response supports the potential role of IVIG in suppressing BKV replication.

However, despite the virological response, only minimal improvement in renal function was observed in our patient. This suggests that irreversible chronic damage, such as interstitial fibrosis and tubular atrophy, may have already developed in the kidney by the time BKVN was diagnosed and treatment initiated. The occurrence of BKVN against a background of significant tubulointerstitial damage explains why functional improvement may be limited even when virological control is achieved.

## Conclusion

In conclusion, this case demonstrates that IVIG may serve as an adjuvant therapy capable of providing virological control in BKVN that is resistant to immunosuppression reduction, but it may be insufficient to reverse established graft damage. Furthermore, the case highlights

the critical importance of proactive screening strategies and patient adherence in preventing irreversible graft injury in the management of BKVN.

## Ethics

**Informed Consent:** Written informed consent was obtained from the patient for this case report.

## Footnotes

### Authorship Contributions

Surgical and Medical Practices: D.E., S.K., F.T., E.E.E., R.Ö., K.U., Concept: D.E., S.K., E.E.E., K.U., Design: D.E., S.K., F.T., R.Ö., K.U., Data Collection or Processing: D.E., S.K., F.T., R.Ö., K.U., Analysis or Interpretation: D.E., E.E.E., R.Ö., K.U., Literature Search: D.E., F.T., E.E.E., Writing: D.E., E.E.E.

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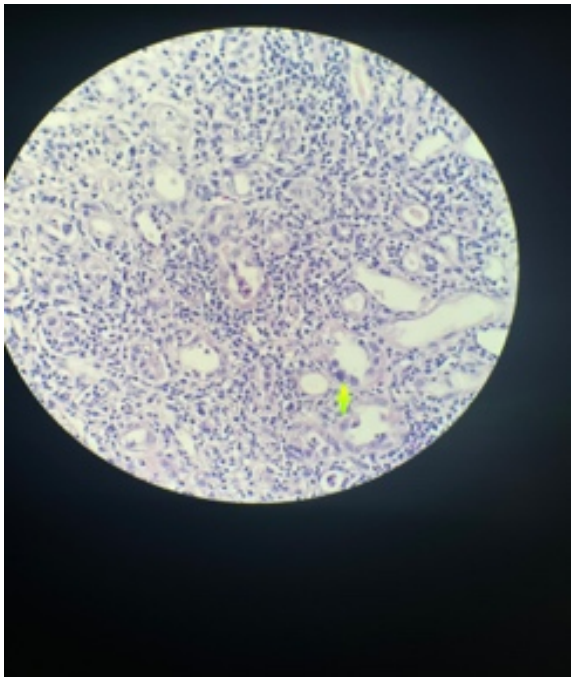

**Figure 1.** Hematoxylin and eosin–stained section showing viral infection, characterized by inclusion bodies in large-nucleated cells lining the tubular epithelium (original magnification × 400).

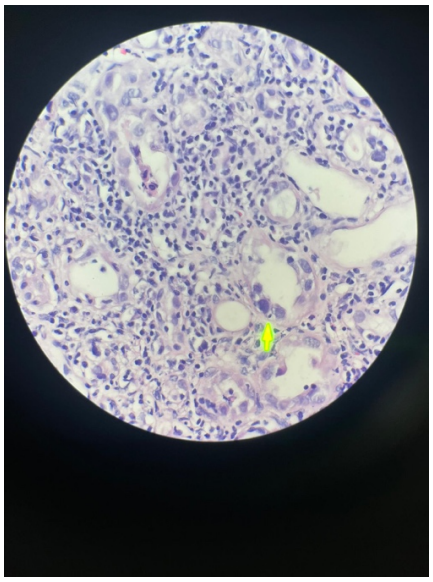

**Figure 2.** Hematoxylin and eosin–stained section demonstrating inclusion bodies in large-nucleated cells affecting the tubular epithelium in viral infection (original magnification × 600).

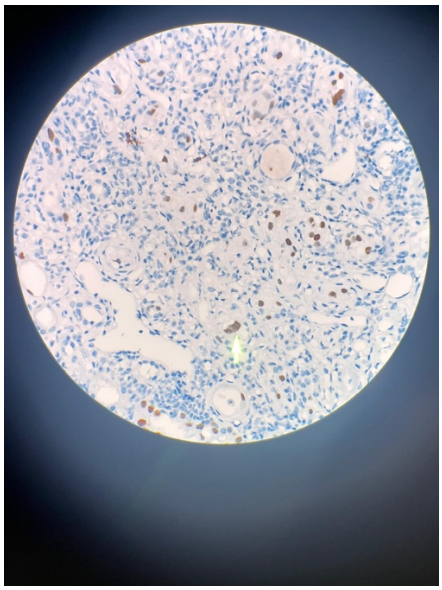

**Figure 3.** BK virus (SV40) immunohistochemical staining showing nuclear positivity in viral structures (original magnification × 600).

**Table 1.** Patient's laboratory results.

| | Admission | First month follow-up | Second month follow-up | Before IVIG | After IVIG |
|---|---|---|---|---|---|
| BKV DNA (PCR) Plasma | 987,870 copies/mL | 704,587 copies/mL | 202,969 copies/mL | 413,255 copies/mL | 162,790 copies/mL |
| BKV DNA (PCR) Urine | 12,747,732,633 copies/mL | 4,666,376,864 copies/mL | 6,656,038,735 copies/mL | 351,117,772 copies/mL | 97,361,574 copies/mL |
| Creatinine | 1.93 mg/dL | 1.94 mg/dL | 2.42 mg/dL | 3.15 mg/dL | 2.83 mg/dL |
| eGFR | 36 mL/min/1.73 $m^2$ | 36 mL/min/1.73 $m^2$ | 28 mL/min/1.73 $m^2$ | 23 mL/min/1.73 $m^2$ | 23 mL/min/1.73$m^2$ |
| Tacrolimus drug level | 3.51 µg/L | 6.47 µg/L | 13.9 µg/L | 9.22 µg/L | 7.84 µg/L |
| Protein/creatinine (spot urine) | 291.67 µg/mg creatinine | 317.99 µg/mg creatinine | 516.74 µg/mg creatinine | 371.26 µg/mg creatinine | 387.23 µg/mg creatinine |

IVIG, intravenous immunoglobulin; eGFR, estimated glomerular filtering rate; BKV, BK virus; PCR, polymerase chain reaction.